ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 26 (2005) 1193 – 1200

The role of the human amygdala in the production of conditioned fear responses

David C. Knight,* Hanh T. Nguyen, and Peter A. Bandettini

Unit on Functional Imaging Methods, Laboratory of Brain and Cognition, National Institute of Mental Health, Building 10, Room 1D80, Bethesda, MD 20892, USA

Received 22 December 2004; revised 10 March 2005; accepted 14 March 2005
Available online 20 April 2005

The amygdala plays a central role in the acquisition and expression of fear memories. Laboratory animal studies indicate that the amygdala both receives sensory information and produces learned behavioral and autonomic fear responses. However, prior functional imaging research in humans has largely focused on amygdala activity elicited by fearful stimuli, giving less attention to this region's role in the production of fear responses. In contrast, the present study used functional magnetic resonance imaging to investigate the amygdala's influence on the generation of conditional fear responses. Significant increases in amygdala activity were observed during the production of conditioned (learning-related), but not orienting, nonspecific, and unconditioned (nonlearning-related) skin conductance responses. Further, greater amygdala activity was demonstrated during conditioned response production than during conditioned stimulus presentation. These results suggest the amygdala not only responds to fearful stimuli, but also generates learning-related changes in human autonomic fear expression. Published by Elsevier Inc.

Keywords: Amygdala; Conditioned fear responses; Skin conductance response; fMRI; Emotion; Arousal; Pavlovian conditioning; Learning and memory

Autonomic responses are a basic component of our emotional reactions to fearful events. Skin conductance response (SCR), an index of electrodermal activity, is one popular psychophysiological measure of autonomic arousal that is often used to monitor emotional expression and fear learning in humans. Insights from lesion, electrical stimulation, and functional imaging studies have identified a core network of brain regions that mediate SCR (Boucsein, 1992; Critchley, 2002; Critchley et al., 2000; Patterson et al., 2002; Williams et al., 2000). A key component of this network is the hypothalamus, which receives cortical input from the ventromedial prefrontal cortex and subcortical projections from the amygdala (Critchley, 2002; Davis, 2000; Öngür and Price, 2000; Patterson et al., 2002). In turn, the hypothalamus projects to brain stem targets that control SCR. A number of other brain regions also influence SCR production. Electrical stimulation of the hippocampus, amygdala, cingulate, and frontal convexities elicit electrodermal changes (Mangina and Beuzeron-Mangina, 1996), while deficits in SCR production have been observed in patients with ventromedial prefrontal, right inferior parietal, and anterior cingulate cortex lesions (Tranel and Damasio, 1994). Further, human functional imaging studies have demonstrated activations within the thalamus, insula, cerebellum, cingulate, ventromedial prefrontal, orbital frontal, and inferior parietal cortices that are correlated with SCR (Critchley et al., 2000; Fredrikson et al., 1998; Nagai et al., 2004; Patterson et al., 2002; Williams et al., 2000). Together, these studies suggest that a core network of brain regions modulates SCR production across a wide variety of cognitive tasks.

Although the amygdala is considered an important component of the neural circuit for emotional expression (Davis 2000; LeDoux, 2000), this region may not be essential for general SCR production. For example, individuals with bilateral amygdala damage produce normal SCRs to a variety of visual and auditory stimuli, and fMRI studies exploring the neuroanatomical mechanisms of SCR production have not observed significant correlations between skin conductance and amygdala activity (Critchley et al., 2000; Patterson et al., 2002; Tranel, 2000; Tranel and Damasio, 1989; Williams et al., 2000). Although the amygdala does not appear necessary for general, nonlearning-related SCR production, this region may be involved in the generation of SCRs specific to certain learning-related processes. Specifically, the amygdala may modulate SCR production during Pavlovian fear conditioning (Bechara et al., 1995; Cheng et al., 2003; Critchley, 2002). In fear conditioning, a conditioned stimulus (CS) predicts an aversive event (unconditioned stimulus: UCS) such as shock or loud noise. Expression of a conditioned response (CR) to the CS is taken as evidence that a CS–UCS association has been learned.

Abbreviations: CS, conditioned stimulus; UCS, unconditioned stimulus; CS+, CS paired with the UCS; CS−, CS presented alone; CR, conditioned response; OR, orienting response; NSR, nonspecific response; UCR, unconditioned response; SCR, skin conductance response.

* Corresponding author. Fax: +1 301 402 1370.
E-mail address: knightd@mail.nih.gov (D.C. Knight).

Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2005.03.020

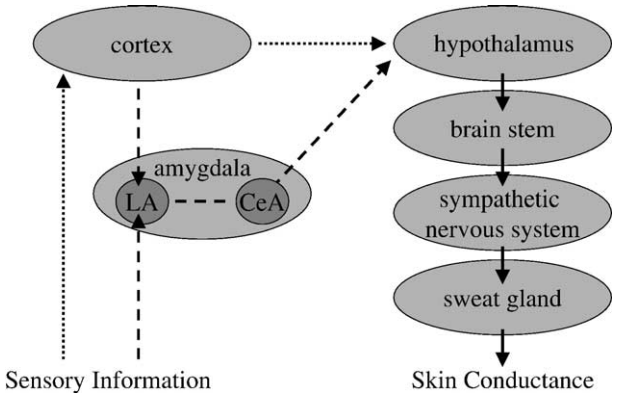

Fig. 1. Pathways believed to mediate general SCR production (dotted lines) and conditioned (learning-related) SCR production (dashed lines). Sensory information is transmitted to the cortex and lateral nucleus of the amygdala (LA). Projections from cortical regions to the hypothalamus appear to play a role in the generation of SCRs across a wide variety of cognitive processes. The LA projects to the central amygdala (CeA) which controls the expression of learned (conditioned fear) SCRs by way of projections to hypothalamus. Solid lines reflect the pathway that is common to both general and conditioned SCR production.

Fear conditioning studies with laboratory animals indicate that sensory information is projected to the lateral amygdala where critical synaptic plasticity takes place, and that projections from the amygdala's central nucleus to brain stem targets control learned behavioral and autonomic fear responses (Davis, 2000; LeDoux, 2000). Thus, the amygdala appears to be crucial for both the acquisition and expression of conditional fear. Therefore, the amygdala may be required for the generation of conditioned SCRs even though it is not necessary for SCRs elicited by other cognitive processes (see Fig. 1). Although most of the research exploring the amygdala's contribution to conditional fear has been conducted with laboratory animals, functional brain imaging studies have also demonstrated this region's involvement in human fear conditioning (Büchel et al., 1998; Cheng et al., 2003; Knight et al., 2004; LaBar et al., 1998). These imaging studies have typically explored amygdala activity elicited by stimulus presentations, and have given less attention to this region's role in the generation of behavioral and autonomic fear responses. Although a few imaging studies have demonstrated a relationship between fear expression and amygdala activity, their ability to differentiate amygdala activation elicited by stimulus presentations from activity associated with fear response production was limited (Büchel et al., 1998; LaBar et al., 1998; Phelps et al., 2001). Further, previous studies have not examined the amygdala's role in the generation of distinct types of SCRs.

The present study investigated the amygdala's role in the production of learning-related changes in SCR by exposing participants to a Pavlovian fear conditioning procedure in which learning-related (conditioned) and nonlearning-related (unconditioned, orienting, and nonspecific) SCRs were evoked (see Fig. 2). One tone (CS+) was repeatedly paired with a loud white-noise UCS, while a second tone (CS−) was presented alone. In addition, a series of novel, non-repeating sounds (Novel) were presented to elicit orienting responses because SCRs to CS− presentations tend to habituate within a few trials. Functional magnetic resonance imaging (fMRI) was used to determine the relationship between

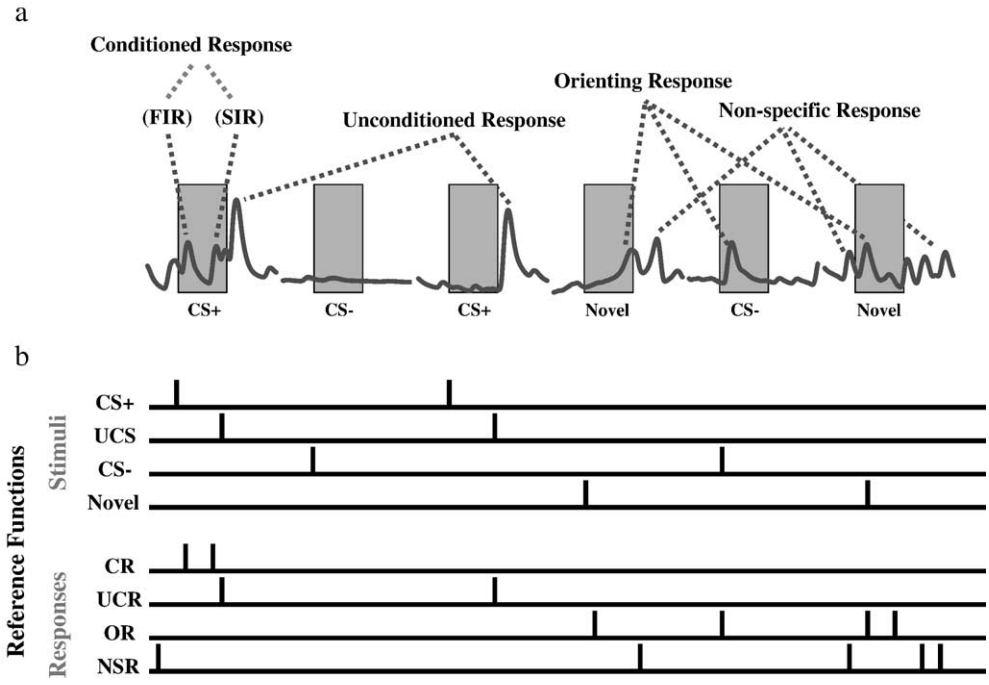

Fig. 2. Examples of skin conductance response (SCR) categorization and corresponding reference waveforms. (a) SCRs that occurred during the 10-s period following onset of the CS+, UCS, and CS−/CSu stimuli were classified as conditioned (CR), unconditioned (UCR), and orienting (OR) responses, respectively. SCRs produced during the inter-trial interval that were not elicited by these stimuli were classified as nonspecific responses (NSR). CRs were further separated into first (FIR) and second (SIR) interval responses. (b) Corresponding reference functions for all stimuli presented and responses evoked. Differences in the timing and occurrence of responses relative to the stimuli that evoke them permit the deconvolution of fMRI time-course data associated with stimulus presentations versus response production.

amygdala activity and the production of learning-related changes in SCR.

Materials and methods

Participants

Nine healthy right-handed volunteers [5 female and 4 male; age (mean ± SEM): 28.33 ± 1.65 years; age range: 23 to 39 years] participated in this study. All subjects provided written informed consent in compliance with the National Institute of Mental Health Institutional Review Board.

Conditioning procedure

Two pure tones (700 and 1300 Hz) were presented as CSs (10 s duration) during the training session. The CS+ (30 trials) co-terminated with a 500-ms loud (100 dB) white-noise (UCS) on 80% of the trials and 20% of the UCS presentations were not paired with any of the CSs. This methodology was selected to permit deconvolution of the fMRI time-course data associated with each stimulus type. The tone serving as the CS− (30 trials) was always presented alone. In addition, 30 non-repeating noises (Novel) consisting of tone sweeps, whistles, and bursts of complex sounds were presented to elicit orienting responses, which tend to habituate relatively quickly to CS− presentations. Further, the 30 Novel stimuli were presented at 5 different durations (2, 4, 6, 8, or 10 s duration) to enhance the orienting responses they evoked. Stimuli were separated by a 20-s inter-trial interval. The tones serving as the CS+ and CS− were counterbalanced and all stimuli were presented in a pseudo-random order such that no more than 2 trials of the same stimulus were consecutively presented.

SCR data acquisition and analysis

A Contact Precision Instruments, skin conductance monitoring system was used to monitor skin conductance response (SCR) throughout the assessment. SCR was sampled (40 Hz) with a pair of surface gel cup electrodes (silver/silver chloride, 6 mm diameter, Biopac model TSD203) attached to the distal phalanx of the middle and ring fingers of the nondominant hand. SCRs that occurred during the 10-s period following onset of the CS+, UCS, and CS−/CSu stimuli were classified as conditioned (CR), unconditioned (UCR), and orienting (OR) responses, respectively (see Fig. 2a). SCRs produced during the ITI that were not elicited by these stimuli were classified as nonspecific responses (NSR). SCRs elicited by CS+, CS−, and Novel stimulus presentations were further separated into first interval responses (FIR: SCR with onset during the 5 s following CS onset) and second interval responses (SIR: SCRs with onset during seconds 6–10 following CS onset). The FIR is often interpreted as an orienting response to CS presentation, whereas the SIR is generally considered an emotional response, elicited by UCS anticipation, that reflects learning the CS–UCS association (Boucsein, 1992; Prokasy and Kumpfer, 1973; Wolter and Lachnit, 1993).

Functional image acquisition and analysis

Structural and functional imaging was completed on a 3-T General Electric Signa scanner using a brain-specific RF head coil (Medical Advances, Milwaukee, WI). Functional imaging of the entire brain was conducted using a gradient-echo echo-planar pulse sequence (TR = 2000 ms, TE = 30 ms, FOV = 24 cm, matrix = 64 × 64, slice thickness = 6 mm) during each of six 470-s blocks of stimulus presentations. High-resolution anatomical images (MPRAGE) were obtained to serve as an anatomical reference. Image processing was performed with the AFNI software package (Cox, 1996; Cox and Hyde, 1997). Echo-planar time series data were motion corrected, concatenated, and reregistered to the fifth volume of the first imaging block (Cox and Jesmanowicz, 1999). Hemodynamic response functions were obtained by deconvolving the input for the onset of all response (CR, OR, NSR, and UCR) and stimulus types (CS+, CS−, Novel, and UCS) from the fMRI time series using a least-squares procedure (see Fig. 2b). The percent area under the second through fourth images of the hemodynamic response curve (AUC) was used as an index of the response magnitude associated with each type of SCR independently. Functional maps reflecting the AUC associated with conditioned, unconditioned, orienting, and nonspecific SCRs were converted to a standard stereotaxic coordinate system and spatially blurred using a 4-mm full-width-at-half-maximum isotropic Gaussian filter (Talairach and Tournoux, 1988). Brain activity associated with each type of SCR (conditioned, orienting, nonspecific, and unconditioned SCRs) was compared to a resting baseline. Regions showing significant responses during the generation of each SCR type were considered to be involved in general SCR production. Those regions showing greater activity associated with conditioned (learning-related) compared to unconditioned, orienting, and nonspecific (nonlearning-related) SCRs were interpreted as regions specifically involved in CR production.

Results

SCR

Comparison of SCRs elicited by CS+ and CS− presentations indicates that the procedure used in this study supports excitatory conditioning. SCRs were separated into first interval response (FIR: SCRs that occur within the first 5 s following CS onset) and second interval response (SIR: SCRs that occur within seconds 6–10 following CS onset) SCRs. The FIRs and SIRs produced during CS+ (mean ± SEM: FIR = 0.14 ± 0.05, SIR = 0.14 ± 0.06) presentations were larger than those elicited by CS− (mean ± SEM: FIR = 0.07 ± 0.03, SIR = 0.05 ± 0.04) trials (FIR: $t[8] = 2.17$, $P < 0.05$; SIR: $t[8] = 2.42$, $P < 0.05$), and indicate subjects learned the CS–UCS relationship. SCRs elicited by CS+ and Novel stimulus presentations did not differ ($t[8] < 1.00$), confirming that presentations of the Novel stimuli had the desired effect of producing large SCRs that were maintained throughout the imaging session (see Fig. 3a). No significant differences in response amplitude were observed between SCRs categorized as conditioned, orienting, nonspecific, and unconditioned responses [$F(1,8) = 1.42$; see Fig. 3b].

fMRI

Brain activation was assessed to identify areas involved in general SCR production as well as those regions that specifically mediate conditioned SCRs. To determine the brain areas involved in general SCR production, we identified regions of overlap that

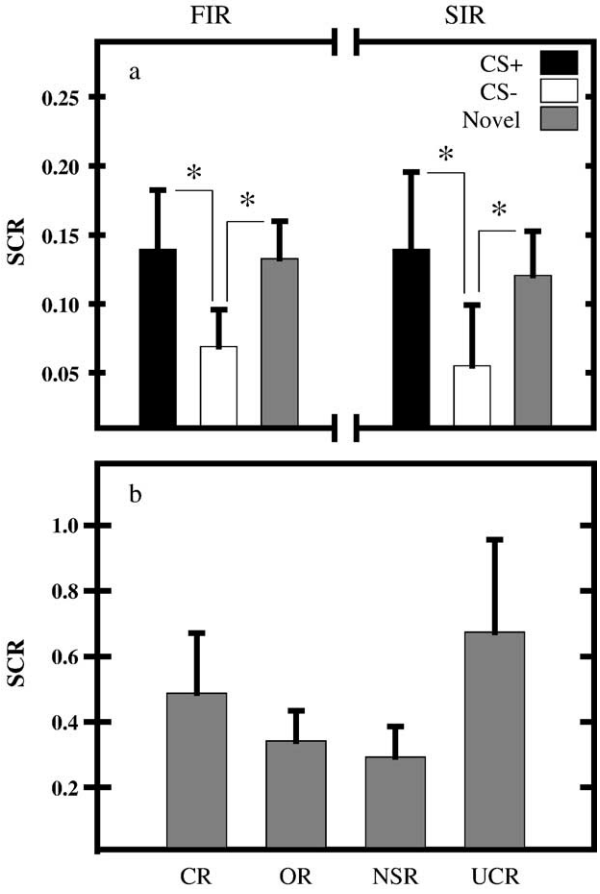

Fig. 3. Skin conductance response. (a) First (FIR) and second (SIR) interval skin conductance responses. Learning-related changes in SCR developed during training such that CS+ presentations elicited larger responses than CS− trials. SCRs produced by CS+ and Novel stimulus presentations did not differ, confirming that Novel stimuli had the desired effect of producing large SCRs throughout the imaging session. (b) The amplitude of SCRs categorized as conditioned (CR), orienting (OR), nonspecific (NSR), and unconditioned (UCR) responses did not differ. Asterisk indicates significant difference at $P < 0.05$.

showed increased activation relative to resting baseline activity during the production of each SCR type. Significant activity was observed within the anterior cingulate, bilateral middle frontal gyrus, bilateral inferior parietal lobule, right superior temporal gyrus, cerebellum, right insula, right putamen, bilateral caudate, and bilateral medial thalamus that was associated with general SCR production (see Table 1a and Fig. 4a). Fig. 4b shows representative time-course data associated with general SCR production from the anterior cingulate. Fig. 4c depicts the area under the hemodynamic response curve (AUC) within the anterior cingulate, which is representative of the pattern of activation observed in other brain regions. There was a significant increase in fMRI signal intensity within each of these regions that was associated with the production of all SCR types.

Regional activation associated with the production of conditioned SCRs was determined by identifying areas that showed greater fMRI signal increases during conditioned SCR production compared to all other SCR types (Table 1b). The pattern of amygdala activation can be seen in Fig. 5a. As seen in Fig. 5b, the amygdala activity associated with conditioned SCRs was larger than that associated with other SCR types. Fig. 5c shows the AUC for each type of SCR categorized, and demonstrates that the magnitude of the amygdala response was significantly larger during the production of conditioned responses compared to orienting, nonspecific, and unconditioned responses. Fig. 5d illustrates the amygdala time-course associated with CR production and CS+ presentation. Activity within this region was larger during the production of CRs than during CS+ presentation. In addition, we explored time-dependent changes in the amygdala response associated with all response (CR, OR, NSR, and UCR) and stimulus (CS+, CS−, Novel, and UCS) types across the six blocks of conditioning trials. No time-dependent changes were observed ($F < 2.36$).

Discussion

Large fMRI signal changes were observed within a number of brain areas during the production of conditioned, orienting, nonspecific, and unconditioned skin conductance responses. These regions included the anterior cingulate, insula, basal ganglia, cerebellum, thalamus, and areas of the prefrontal, temporal, and parietal cortices (see Fig. 4 and Table 1a). Previous studies exploring the neural mechanisms of SCR production have observed activations within many of these areas (Critchley et al., 2000; Fredrikson et al., 1998; Nagai et al., 2004; Patterson et al., 2002; Williams et al., 2000). The current results, in conjunction with prior findings, suggest these brain regions mediate general SCR production across a wide variety of cognitive tasks. In contrast, the amygdala activity observed in the present study was specifically associated with the generation of conditioned (learning-related), but not orienting, nonspecific, or unconditioned (nonlearning-related) changes in SCR production. These results suggest that the amygdala produces learned fear responses. Further, larger amygdala responses were detected during CR expression than CS+ presentation, indicating the observed activity was more closely related to fear expression than to processing the properties of fearful stimuli (see Fig. 5).

Prior laboratory animal and human functional imaging research has suggested that the amygdala responds to novelty and may be involved in the generation of orienting responses (Holland and Gallagher, 1999; Knight et al., 2004; Rollins et al., 2001; Wright et al., 2003). However, novel stimuli and the SCRs they produced in the present study were not associated with amygdala activation. This finding may be related to differences in the neural circuits that mediate orienting to novelty or salient stimulus features in a bottom–up manner as opposed to orienting as a top–down process that is related to the learned significance of stimuli. The amygdala appears to be involved in orienting to stimuli that have acquired significance through their predictive relationships with other events, whereas aspects of orienting that are entirely stimulus-driven do not appear to rely upon the amygdala (Holland and Gallagher, 1999). Recent fMRI fear conditioning research has observed amygdala activity that may reflect orienting processes induced by changes to the predictive relationship between the CS and UCS that were learned during training (Knight et al., 2004). In contrast, the novel stimuli presented in the present study were designed to engage bottom–up orienting processes that may not rely upon circuitry that includes the amygdala (Holland and Gallagher, 1999; Tranel and Damasio, 1989).

Previous studies investigating the effect of human brain lesions on autonomic expression are consistent with the view that

Table 1
Activity associated with SCR production

Location	Hemisphere	Coordinates (RL, AP, IS)	Volume (mm^3)	*t* value	*P* value
(a) Activity associated with general SCR production					
Anterior cingulate		0, 6, 37	2717	8.554	5×10^{-11}
Middle frontal gyrus	Right	28, 37, 28	257	5.885	5×10^{-7}
	Left	−27, 48, 24	388	5.578	5×10^{-7}
Superior temporal gyrus	Right	51, 30, 4	353	6.293	5×10^{-8}
Insula	Right	29, 7, 7	168	8.460	5×10^{-11}
Inferior parietal lobule	Right	54, −37, 25	309	4.776	5×10^{-5}
	Left	−52, 39, 23	1057	6.580	5×10^{-8}
Thalamus	Right	10, 20, 2	192	6.519	5×10^{-8}
	Left	−13, 19, 5	244	7.024	5×10^{-9}
Caudate	Right	16, 8, 8	892	8.448	5×10^{-11}
	Left	−10, 12, 10	250	7.817	5×10^{-9}
Putamen	Right	29, −16, 4	551	8.314	5×10^{-11}
Cerebellum	Right	7, −48, −19	345	6.722	5×10^{-9}
(b) Activity associated with conditioned SCR production					
Amygdala	Right	28, −7, −15	147	5.103	5×10^{-5}
Insula	Right	40, −7, −4	401	5.801	5×10^{-5}
Cerebellum	Right	15, −50, −24	336	4.828	5×10^{-3}
Medial prefrontal cortex	Left	−10, 32, 38	396	5.188	5×10^{-5}
		−12, 21, 45	139	6.173	5×10^{-5}
		−11, 4, 52	179	4.258	5×10^{-3}
Middle frontal gyrus	Left	−27, −8, 41	596	5.539	5×10^{-5}
Precentral gyrus	Left	−12, −23, 64	572	5.298	5×10^{-5}
		−29, −27, 47	670	4.813	5×10^{-3}
		−55, −9, 35	632	6.922	5×10^{-5}
STG	Left	−58, −15, 5	179	6.039	5×10^{-5}

Locations, volumes, and Talairach coordinates (Talairach and Tournoux, 1988) for the centers-of-mass of contiguous activation. RL, right/left; AP, anterior/posterior; IS, inferior/superior.

amygdala function influences autonomic activity (Asahina et al., 2003; Tranel, 2000). However, these studies differ on the precise role played by the amygdala in the generation of SCRs. Asahina et al. (2003) observed complete SCR disruption in a patient with bilateral amygdala lesions, suggesting that this region contributes to the general production of SCR. In contrast, work by Tranel

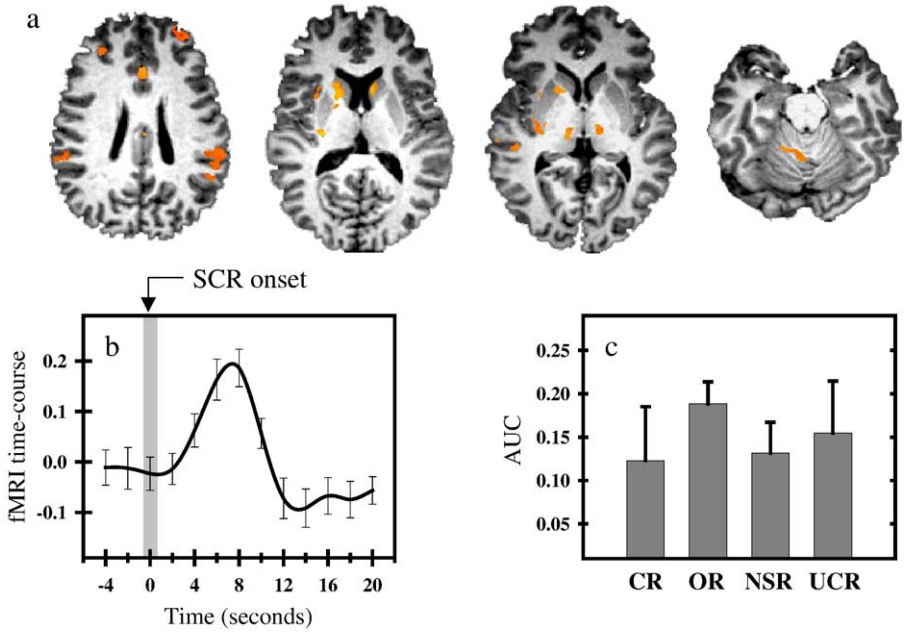

Fig. 4. Brain activation associated with general SCR production. (a) Regions in which large hemodynamic responses were observed during the production of all SCR types. (b) Functional MRI time-course (% of baseline) for anterior cingulate activity associated with the general production of all SCRs. (c) Area under the hemodynamic response curve (AUC) within the anterior cingulate as a percentage of baseline activity for conditioned (CR), orienting (OR), nonspecific (NSR), and unconditioned (UCR) responses.

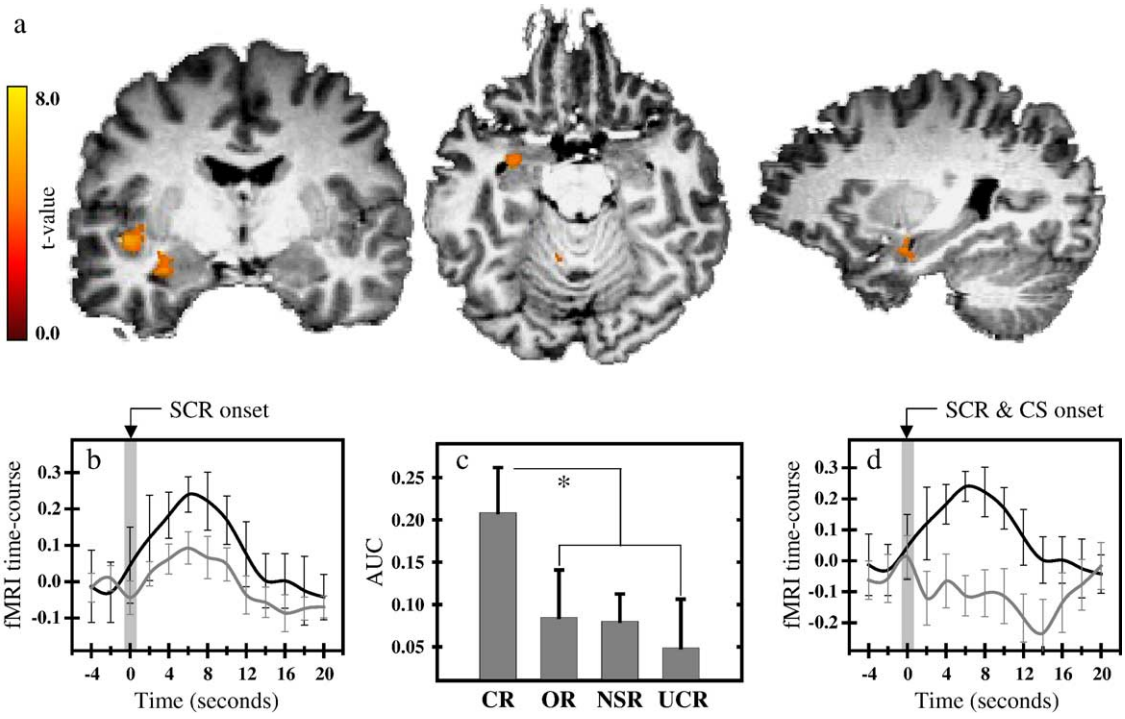

Fig. 5. Brain activation associated with conditioned SCR production. (a) Coronal, axial, and sagittal views of right amygdala and insula (coronal view) activation. (b) Functional MRI time-course (% of baseline) for amygdala activity associated with the production of conditioned (CR) SCRs (black line) and all other (orienting: OR, nonspecific: NSR, and unconditioned: UCR) SCR types (gray line). (c) Area under the hemodynamic response curve (AUC) as a percentage of baseline activity for CRs, ORs, NSRs, and UCRs. (d) Functional MRI time-course (% of baseline) for amygdala activity associated with the production of conditioned SCRs (black line) and CS+ presentations (gray line). Asterisk indicates significant difference at $P < 0.05$.

(2000) indicates that amygdala lesions disrupt conditioned SCRs, but leave other types of SCRs relatively intact. Results from the present study support the findings by Tranel (2000) that suggest the amygdala is primarily involved in the production of learned fear responses. Further, the present findings are consistent with laboratory animal studies that indicate the amygdala is an important component of the neural circuit that mediates fear learning and memory (Davis, 2000; LeDoux, 2000). Afferent projections carrying information about the CS and UCS converge within the lateral amygdala, and central nucleus projections to brainstem targets are important for the expression of learned autonomic and behavioral fear responses (Davis, 2000; Helmstetter, 1992; LeDoux, 2000; Price and Amaral, 1981). These studies indicate the amygdala is not only involved in the formation of CS–UCS associations, but is also crucial for the expression of conditional fear.

Although most of the research exploring the amygdala's contribution to conditional fear has been conducted with laboratory animals, functional brain imaging studies have also demonstrated this region's involvement in human fear conditioning (Büchel et al., 1998; Cheng et al., 2003; Knight et al., 2004; LaBar et al., 1998). These fMRI studies have largely focused on the amygdala's response to stimulus presentations. Although learning-related amygdala activity was observed, these studies did not include reference waveforms reflecting properties of the CR (Büchel et al., 1998; Knight et al., 2004; LaBar et al., 1998). Thus, activity associated with CS+ presentation and CR production could not be differentiated. Even though less emphasis has been placed on the amygdala's role in human fear expression, a few studies have observed a relationship between learning-related changes in SCR and amygdala activity (Büchel et al., 1998; Cheng et al., 2003; LaBar et al., 1998; Phelps et al., 2001). For example, decreases in SCR amplitude appear to parallel the attenuation of amygdala responses to CS+ presentations across the conditioning session (Büchel et al., 1998; LaBar et al., 1998). Although similar time-dependent changes were not observed in the present study, the inclusion of reference vectors that reflect CR production may have accounted for variance in the fMRI signal that went unexplained in previous work.

Other recent functional imaging research supports the view that amygdala activity does not merely represent the formation of CS–UCS associations, but also reflects CR expression (Cheng et al., 2003, 2004). The present study extends this prior work by distinguishing the amygdala's role in the generation of distinct types of SCRs and by separating the amygdala response to CS+ presentation from that associated with CR production. Although there is significant overlap between the CS+ and CR, the inherent variability in the timing and occurrence of SCRs is sufficient to distinguish amygdala responses to CS+ presentations from activity associated with CR production. In the present study, amygdala activity related to CR expression was greater than that related to CS+ presentation. This finding suggests that the observed activity is more closely related to aspects of fear expression than to processing properties of fearful stimuli. Further, SCRs elicited by nonlearning-related processes (i.e., orienting, nonspecific, and unconditioned responses) were not associated with increased amygdala activity. Therefore, the observed amygdala activation does not appear to be involved in simple response production. These data provide further

evidence of the amygdala's involvement in human Pavlovian fear conditioning, and demonstrate this region's role in the production of learning-related fear responses.

Right, but not left amygdala activity was associated with CR production in the present study. This finding is consistent with the unilateral activation of the right amygdala often observed in fMRI fear conditioning research (Büchel et al., 1998; Cheng et al., 2003; Knight et al., 2004; LaBar et al., 1998). Bilateral and unilateral left amygdala activations have also been observed in fear learning studies (Büchel et al., 1999; Morris et al., 1998; Phelps et al., 2001). Left amygdala activity has often been attributed to higher-level cognitive processes (Morris et al., 1998; Phelps et al., 2001). However, a recent review of emotional processing and the human amygdala found that none of the traditional models of hemispheric specialization adequately explain the lateralization of amygdala activity that is often observed in imaging studies (Zald, 2003). Prior fMRI research investigating amygdalar interhemispheric functional connectivity indicates that the left and right amygdala are functionally independent (Irwin et al., 2004). Further, the left and right amygdala appear to have distinct patterns of functional connectivity with prefrontal brain regions (Irwin et al., 2004; Knight et al., 2005). These findings suggest that hemispheric differences in frontocortical–amygdala interactions may account for the unilateral amygdala activity demonstrated in many functional imaging studies of emotional learning.

In conclusion, the present study used fMRI to investigate brain activity associated with learning-related changes in SCR production. Large event-related signal changes were demonstrated within the amygdala during the production of conditioned SCRs, whereas limited activation of this region was detected during the generation of other SCR types (i.e., orienting, nonspecific, or unconditioned responses). The observed amygdala activity was closely associated with CR production, but not CS+ presentation, indicating that this activity better reflects properties of the CR than aspects of stimulus input. These findings indicate that the amygdala plays a significant role in the production of learned fear responses.

References

Asahina, M., Suzuki, A., Mori, M., Kanesaka, T., Hattori, T., 2003. Emotional sweating response in a patient with bilateral amygdala damage. Int. J. Psychophysiol. 47, 87–93.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., Damasio, A.R., 1995. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus. Science 269, 1115–1118.

Boucsein, W., 1992. Electrodermal Activity. Plenum Press, New York.

Büchel, C., Morris, J., Dolan, R.J., Friston, K.J., 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron 20, 947–957.

Büchel, C., Dolan, R.J., Armony, J.L., Friston, K.J., 1999. Amygdala–hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. J. Neurosci. 19, 10869–10876.

Cheng, D.T., Knight, D.C., Smith, C.N., Stein, E.A., Helmstetter, F.J., 2003. Functional MRI of human amygdala activity during Pavlovian fear conditioning: stimulus processing versus response expression. Behav. Neurosci. 117, 3–10.

Cheng, D.T., Knight, D.C., Smith, C.N., Stein, E.A., Helmstetter, F.J., 2004. Autonomic Fear Responses and Human Amygdala Activity: An Event-Related FMRI Study. Pavlovian Society Meeting, Baltimore, MD.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.

Cox, R.W., Hyde, J.S., 1997. Software tools for the analysis and visualization of fMRI data. NMR Biomed. 10, 171–178.

Cox, R.W., Jesmanowicz, A., 1999. Real-time 3D image registration for functional MRI. Magn. Reson. Med. 42, 1014–1018.

Critchley, H.D., 2002. Electrodermal responses: what happens in the brain. Neuroscientist 8, 132–142.

Critchley, H.D., Elliot, R., Mathias, C.J., Dolan, R.J., 2000. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. J. Neurosci. 20, 3033–3040.

Davis, M., 2000. The role of the amygdala in conditioned and unconditioned fear and anxiety. In: Aggleton, J.P. (Ed.), The Amygdala: a Functional Analysis, 2nd ed. Oxford Univ. Press, New York, pp. 213–287.

Fredrikson, M., Furmark, T., Olsson, M.T., Fischer, H., Andersson, J., Långström, B., 1998. Functional neuroanatomical correlates of electrodermal activity: a positron emission tomographic study. Psychophysiology 35, 179–185.

Helmstetter, F.J., 1992. Contribution of the amygdala to learning and performance of conditional fear. Physiol. Behav. 51, 1271–1276.

Holland, P.C., Gallagher, M., 1999. Amygdala circuitry in attentional and representational processes. Trends Cogn. Sci. 3 (2), 65–73.

Irwin, W., Anderle, M.J., Abercrombie, H.C., Schaefer, S.M., Kalin, N.H., Davidson, R.J., 2004. Amygdalar interhemispheric functional connectivity differs between the non-depressed and depressed human brain. NeuroImage 21, 674–686.

Knight, D.C., Smith, C.N., Cheng, D.T., Stein, E.A., Helmstetter, F.J., 2004. Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. Cogn. Affect. Behav. Neurosci. 4, 317–325.

Knight, D.C., Nguyen, H.T., Bandettini, P.A., 2005. Differences in the functional connectivity of the left and right amygdala. Organization for Human Brain Mapping 11th Annual Meeting, Toronto, Canada.

LaBar, K.S., Gatenby, C., Gore, J.C., LeDoux, J.E., Phelps, E.A., 1998. Human amygdala activation during conditioned fear acquisition and extinction: a mixed trial fMRI study. Neuron 20, 937–945.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184.

Mangina, C.A., Beuzeron-Mangina, J.H., 1996. Direct electrical stimulation of specific human brain structures and bilateral electrodermal activity. Int. J. Psychophysiol. 22, 1–8.

Morris, J.S., Ohman, A., Dolan, R.J., 1998. Conscious and unconscious learning in the human amygdala. Nature 393, 467–470.

Nagai, Y., Critchley, H.D., Featherstone, E., Trimble, M.R., Dolan, R.J., 2004. Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a "default mode" of brain function. NeuroImage 22, 243–251.

Öngür, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219.

Patterson II, J.C., Ungerleider, L.G., Bandettini, P.A., 2002. Task-independent functional brain activity correlation with skin conductance changes: an fMRI study. NeuroImage 17, 1797–1806.

Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. Nat. Neurosci. 4, 437–441.

Price, J.L., Amaral, D.G., 1981. An autoradiographic study of the projections of the central nucleus of the monkey amygdala. J. Neurosci. 1, 1242–1259.

Prokasy, W.F., Kumpfer, K.L., 1973. Classical conditioning. In: Prokasy, W.F., Raskin, D.C. (Eds.), Electrodermal Activity in Psychological Research. Academic Press, New York, pp. 157–202.

Rollins, B.L., Stines, S.G., McGuire, H.B., King, B.M., 2001. Effects of amygdala lesions on body weight, conditioned taste aversion, and neophobia. Physiol. Behavi. 72, 735–742.

Tranel, D., 2000. Electrodermal activity in cognitive neuroscience. In: Lane, R.D., Nadel, L. (Eds.), Cognitive Neuroscience of Emotion. Oxford Univ. Press, New York, pp. 192–224.

Tranel, D., Damasio, H., 1989. Intact electrodermal skin conductance responses after bilateral amygdala damage. Neuropsychologia 27, 381–390.

Tranel, D., Damasio, H., 1994. Neuroanatomical correlates of electrodermal skin conductance responses. Psychophysiology 31, 427–438.

Williams, L.M., Brammer, M.J., Skerrett, D., Lagopolous, J., Rennie, C., Kozek, K., Olivieri, G., Peduto, T., Gordon, E., 2000. The neural correlates of orienting: an integration of fMRI and skin conductance orienting. NeuroReport 11, 3011–3015.

Wolter, J., Lachnit, H., 1993. Are anticipatory first and second interval skin conductance responses indicators of predicted aversiveness? Int. Physiol. Behav. Sci. 28, 163–166.

Wright, C.I., Martis, B., Schwartz, C.E., Shin, L.M., Fischer, H., McMullin, K., Rauch, S.L., 2003. Novelty responses and differential effects of order in the amygdala, substantia innominata, and inferior temporal cortex. NeuroImage 18, 660–669.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, New York.

Zald, D.H., 2003. The human amygdala and the emotional evaluation of sensory stimuli. Brain Res. Rev. 41, 88–123.